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Diabetes mellitus and venous thromboembolism: A systematic review and meta-analysis

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Abstract

Diabetes mellitus (DM) may be a risk factor for venous thromboembolism (VTE) but results are inconsistent.

Aim—We conducted a systematic review and meta-analysis of epidemiologic studies to quantify the association between DM and VTE.

Methods and results—We included studies identified in PubMed, Web of Science, and CINAHL through 07/31/2014. We identified 19 studies that met our selection criteria. We pooled RRs using a random-effects model: the pooled RR for the association of DM with VTE was 1.10 (95% CI: 0.94–1.29). Between-study heterogeneity was explored with a forest plot, funnel plot, meta-regression, and a stratified analysis. Between-study heterogeneity was observed and not explained by study design, method of DM assessment, or degree of adjustment for confounding. Sensitivity analyses omitted one study at a time to assess the influence of any single study on the pooled estimate. These analyses indicated that one large study was highly influential; when this study was excluded, the pooled estimate increased and just reached statistical significance: 1.16 (95% CI: 1.01–1.34)].

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

E.J.B. formulated the research questions, conducted the search and analyses, and wrote the manuscript. A.R.F. formulated the research questions and reviewed/edited the manuscript. P.L.L., E.S., and M.C. reviewed/edited the manuscript. N.A.Z. conducted analyses and reviewed/edited the manuscript. A.A. provided guidance and reviewed/edited the manuscript. E.J.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conclusions—This meta-analysis suggests either no association or a modest positive one between DM and VTE in the general population. DM is unlikely to play a major role in VTE development.

Keywords

diabetes mellitus; venous thromboembolism; systematic review; meta-analysis

1.1 Introduction

Diabetes mellitus (DM) has been proposed as a risk factor for venous thromboembolism (VTE). However, reported associations of DM with VTE are inconsistent, and many estimates from previous studies have not accounted for the potential confounding effect of obesity. Two previous systematic reviews each estimated a 1.4-fold increased risk of VTE for persons with DM compared to persons without[1,2]. However, neither analysis adequately accounted for potential confounders of the DM-VTE association, making it difficult to know whether the observed increased risk in VTE is due to other VTE risk factors associated with DM. Further, some research studies, both published[3–7] and unpublished, were not included in either review. Thus, we undertook this systematic review and meta-analysis to update the current state of the literature and rigorously quantify the association between DM (type 1 or 2) and VTE [deep vein thrombosis (DVT) or pulmonary embolism (PE)]. We hypothesized that DM would be positively associated with VTE before and after adjustment for potential confounding variables, including obesity.

1.2 Methods

We followed the Meta-analysis of Observational Studies in Epidemiology Guidelines[8] throughout this review.

1.2.1 Data Sources and Searches

Investigator E.J.B. consulted with a biomedical librarian to develop the search strategy. E.J.B. searched PubMed, Web of Science, and CINAHL databases. The database search included both keywords and headings, explosion searching, and truncated words related to diabetes mellitus, venous thromboembolism, pulmonary embolism, and deep vein thrombosis. The search cutoff date was July 31, 2014. No language restrictions were applied. We queried experts to identify additional studies, including unpublished material. We did not include grey literature. We manually searched reference lists of review articles and eligible articles to identify additional eligible studies.

1.2.2 Study Selection

Studies were included in this review if they 1) were case-control or cohort design and 2) reported an effect estimate between DM (any definition - including self-report, glucose measurement, or medical records) and VTE (defined as DVT and/or PE) in humans or provided enough information to calculate an effect estimate and its standard error. Studies were excluded if 1) they had no original data; 2) DVTs were outside of the leg (PE not excluded), because risk factors can differ depending on where the DVT occurs; 3) VTEs

were solely recurrent, because risk factors can be different for a recurrent versus first-time VTE; or 4) the entire study population was affected by a specific medical condition (e.g. cancer) or a procedure, because we were interested in studies that were broadly representative of general populations.

1.2.3 Data Extraction and Quality Assessment

We abstracted estimates of association (odds ratios, relative risks, or hazard ratios) between DM and VTE, and their standard errors. When a standard error was not reported, it was derived from data provided in the article. Since VTE is relatively rare, odds ratios and hazard ratios were likely reasonable estimates of the relative risks (RRs)[9]. Thus, we represented and interpreted all effect estimates as RRs for this review.

In each included study, we sought to abstract the estimate with the most complete adjustments for potential confounders. We considered an effect estimate as adequately controlled for potential confounders if the study statistically adjusted for age, BMI, and race (or only involved primarily one race group, defined as a study population with ≥80% of a single race). Age, and BMI, and race were required as the minimal adjustment set because we considered them the most likely confounders of the association of DM with VTE, since they are established risk factors for VTE and associated with DM[10–17]. We queried corresponding authors to obtain missing information or results that were more fully adjusted. In the situation of multiple articles from the same study, the article that had the most complete adjustments for potential confounding was used.

1.2.4 Data Synthesis and Analysis

We tabulated the eligible studies and described their characteristics. We investigated the degree of heterogeneity in effect estimates between studies by generating three forest plots: One included all unique study samples, and the other two stratified by VTE type [provoked (defined as VTE occurring in a patient with an antecedent transient acquired risk factor for VTE) and unprovoked VTE]. Because of substantial qualitative and quantitative heterogeneity across studies, a random-effects[18] model was used to pool the effect estimates. We reported statistical tests for between-study heterogeneity: 1) An overall homogeneity test p-value from Cochran's Q statistic[18] and 2) I^2, a measure of the percentage of heterogeneity that was due to between-study differences, as opposed to sampling variation[19]. We considered statistical significance of Cochran's Q statistic as a p-value of <0.1 due to the test's low power[20]. We interpreted an I^2 value of 25–50% as low heterogeneity, 50–75% as moderate heterogeneity, and ≥75% as high heterogeneity.

To assess potential publication bias, we generated a funnel plot[20] to provide a visual assessment of whether treatment effects were associated with study size (manifested as funnel plot asymmetry). We used a fixed-effects model to produce the funnel plot since results are less affected than random-effects when publication bias is present[20]. We also statistically checked for funnel plot asymmetry using the Begg[21] and Egger tests[22].

We ran meta-regressions to examine heterogeneity between studies by regressing the log RR on several pre-specified study characteristics: study design (case-control; cohort), level of confounding (controlled for age, BMI, and race; not controlled), and objective measurement

of DM (included glucose measurement; no glucose measurement). Because a fixed-effects meta-regression requires the strong assumption that all heterogeneity can be explained by the covariates in the model[23,24], we used a random-effects model[25]. The Knapp-Hartung[26] variance estimator was used, as it produces a false-positive rate close to the nominal value of .05[23]. Therefore, statistical significance was considered $p < 0.05$ for the meta-regressions. We calculated ratios of RRs and their 95% CIs from the meta-regressions, which is a ratio of the average RR in studies with one characteristic to the average RR of studies with another characteristic. Within strata of the same pre-specified study characteristics, we also calculated a random-effects pooled RR, and corresponding homogeneity p-value and I^2.

We performed sensitivity analyses, omitting one study at a time to assess the influence of any single study on the pooled estimate. All statistical analyses were conducted using Stata software, version 12.1.

1.3 Results

We identified 2,224 publications through PubMed, 389 through CINAHL, and 1,727 through Web of Science (these numbers include overlap). Of these publications, eight publications met the inclusion criteria[4,5,27–32] (See supplemental Figure S1 for flow diagram and supplemental Table S1 for exclusion log). We further identified 8 publications[3,6,7,33–37] through manual review of reference lists of eligible articles and review articles[1,2,38–42]. Additionally, we obtained previously unpublished results from 3 studies through querying experts (queried A.R.F. and P.L.L.) [de novo analysis: Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study [43]; re-analysis with additional follow-up time: Cardiovascular Health Study (CHS)[44] and the Atherosclerosis Risk in Communities (ARIC) study[45]].

In all, 19 unique studies met the selection criteria for this review: 11 cohort studies and 8 case-control studies. More-fully-adjusted RRs than originally published were obtained by author queries for 4 studies[6,27,30,34]. Supplementary Table S2 describes notable details of data abstraction from all studies, and analyses of unpublished data.

Tables 1 and 2 report the characteristics of cohort and case-control studies included in the review. Most studies (84%) were conducted in the United States or Scandinavia. Most (82%) of the cohort studies were population-based, whereas most (75%) of the case-control studies were hospital or clinic-based. The number of VTE events per study varied widely: from 38 to 2,137. Measurement of DM varied across studies, but just over half of studies relied on self-report only, while others used some variation of criteria including fasting or non-fasting glucose levels, physician diagnosis, oral glucose tolerance test, or use of DM medication. Notably, Sveinsdottir et al.[36] defined DM as fasting glucose ≥ 6.1 mmol/l, whereas many other studies that used fasting glucose defined DM as ≥ 7 mmol/l. One study did not specify its method of DM measurement[5]. No study specifically distinguished between type 1 and type 2 DM, but presumably studies contained mostly type 2, given that the vast majority of cases of DM in adults are type 2. Most (74%) studies relied on imaging techniques to measure VTE; the rest relied solely on International Classification of Diseases

codes. Just more than half of studies controlled for age, BMI, and race: Only 2 out of 19 did not control for age[4,46], 8 did not control for BMI[3–5,7,32,33,35,37], and 1 did not control for race[6] (Figure 1).

Comparing those with DM to those without, the pooled RR for VTE was 1.10 (95% CI: 0.94–1.29) (Figure 1). Figure 1 encompasses all 19 unique studies; 17 used total (provoked plus unprovoked) VTE as the outcome, whereas 2 used unprovoked VTE only as the outcome[6,37]. Five studies also reported RR estimates for provoked VTE, and 8 for unprovoked. The pooled RR for provoked VTE only was 1.02 (95% CI: 0.75–1.39) (supplemental Figure S2), and for unprovoked was 1.03 (95% CI: 0.68–1.57) (supplemental Figure S3).

There were moderate levels of statistical heterogeneity in findings from the 19 unique studies of DM and VTE (I^2=59.7%, Cochran's Q p-value <0.0005), and between the 8 studies of DM and unprovoked VTE (I^2=66.1%, Cochran's Q p-value = 0.004). We observed low to moderate levels of heterogeneity between the 5 studies of DM and provoked VTE (I^2=45.5%, Cochran's Q p-value = 0.12). To evaluate potential sources of heterogeneity, we conducted pre-specified subgroup analyses that compared the RR estimates for studies by study design, method of DM measurement, and level of control for potential confounding variables (supplemental Table S3). No significant differences in RRs were observed. Using all 19 studies, there was no indication of publication bias, as evidenced by non-significant Begg and Egger tests (p=0.12 and 0.25, respectively) and a relatively symmetric funnel plot (supplemental Figure S4).

Sensitivity analyses indicated that the REGARDS Study influenced the pooled estimate more than other studies (Figure 2). When we excluded the REGARDS Study, the pooled estimate increased slightly and just reached statistical significance [including REGARDS: 1.10 (95% CI: 0.94–1.29; excluding REGARDS: 1.16 (95% CI: 1.01–1.34)]. Although there was less statistical heterogeneity after excluding REGARDS, some heterogeneity did remain [including REGARDS: I^2=59.7%, Cochran's Q p-value <0.0005; excluding REGARDS: I^2=48.3%, Cochran's Q p-value = 0.01].

1.4 Discussion

This systematic review and meta-analysis of published and unpublished studies suggests either no association or a very small positive association between DM and venous thromboembolism in the general population. Between-study heterogeneity was observed and not explained by study design, method of DM measurement, or level of adjustment for confounding. There was no evidence of publication bias.

The findings of our meta-analysis contradict two previous meta-analyses. Both estimated a 1.4-fold increased risk of VTE for persons with diabetes compared to persons without[1,2]. However, the 2008 meta-analysis[1] did not account for age, BMI, or race as potential confounding variables to the diabetes-VTE relation, making results difficult to interpret. Potential confounding was also an issue in the 2014 meta-analysis[2]: Three quarters of the studies included did not adjust for BMI. For the present meta-analysis, we queried

corresponding authors of included studies that did not account for body size (n=11), asking for BMI-adjusted estimates. We received BMI-adjusted estimates for 4 studies. Three out of 4 of these studies were included, without adjustment for BMI, in the 2014 meta-analysis; we wondered whether substituting the unadjusted for BMI-adjusted estimates would impact their results. It did: the 2014 meta-analysis reported a pooled effect estimate of 1.36 (95% CI: 1.11–1.68) for analyses restricted to high-quality cohort studies, but when we substituted the 3 more fully-adjusted estimates, the positive association decreased to 1.24 (95% CI: 0.96–1.61), and lost statistical significance (Details of analysis in supplemental Table S4).

A sensitivity analysis indicated that the REGARDS Study was highly influential. The REGARDS Study - a large, prospective cohort study of whites and African Americans across the United States - reported an inverse association between DM and VTE [0.65 (95% CI: 0.46–0.91)]. The surprising inverse association could be at least partly explained by REGARDS' VTE ascertainment methods, which possibly led to biased ascertainment of VTE. REGARDS predominantly captured VTE events through participant report; participants were queried in 2010–11 about past VTE events (as far back as 2003)[43]. Similar questionnaires have 98% specificity and >70% sensitivity for ascertaining VTE[47]. Then, medical records were retrieved so that potential VTE events could be validated. Notably, not all records could be retrieved, and the retrieval rate differed by race (79.5% overall retrieval rate, 72% among African Americans, 85% among whites)[43]. Thus, VTE ascertainment in REGARDS was not complete, and it is difficult to know how factors associated with under-ascertainment might bias an association between DM and VTE.

There is methodologic variation in the measurement of DM and VTE across studies. Many studies rely on self-reported DM, which is a specific (95.6% to 96.8%, depending on the reference definition), but not sensitive (58.5% to 70.8%) measure of DM[48]. As this DM misclassification does not likely differ by VTE status, we expect this misclassification to drive estimates of the DM-VTE relation towards the null. Some studies rely solely on International Classification of Diseases codes to measure VTE; previous work comparing VTE codes to medical records has found the codes to be reasonably valid indicators of VTE hospitalization[49].

We chose to examine the relation between DM and VTE because DM has been proposed as a risk factor for VTE, the theoretical mechanism being that hyperglycemia contributes to elevated coagulation factors, impaired fibrinolysis, and increased likelihood of thrombosis[40,50]. Indeed, laboratory evidence suggests that high glucose levels 1) increase oxidative stress, which in turn increases gene transcription of coagulation factors; 2) degrade the glycocalyx layer of the endothelial wall, which releases coagulation factors and stimulates the coagulation cascade; and 3) increase glycation of proteins involved in coagulation and fibrinolysis, shifting their activity towards a procoagulant state[40]. However, our findings suggest that DM is unlikely to play a major role in VTE development.

This review extends the current literature, particularly since we included three large, unpublished data sources and more comprehensively accounted for potential confounders of the DM-VTE relation. Our review and analysis also has limitations that warrant discussion.

We observed substantial qualitative and quantitative heterogeneity across studies, but could not explain it. Future research should attempt to pinpoint sources of heterogeneity; an individual participant data meta-analysis would be a particularly good design to explore heterogeneity, as this would remove heterogeneity from analyses, and meta-regressions could use patient-level (as opposed to study-level) data. And, finally, this review drives home the importance of accounting for potential confounding variables when examining the relation of DM with VTE, especially BMI. Notably, biases of the effect estimates likely remain even under our definition of an "adequately controlled" effect estimate. These biases were probably related to methods of measurement (e.g., estimating BMI using self-report versus direct measurement) and modeling (e.g., modeling age as bands versus continuous) variables. Incomplete control of confounding of a DM-VTE relation by BMI and age would likely bias an estimate upwards. Other VTE risk factors (e.g.: age, race, cancer, hormone therapy, oral contraceptives, smoking, sex, and pregnancy) also deserve consideration as confounding variables in future investigations of the relation between diabetes and VTE.

In conclusion, this literature-based meta-analysis supports a very modest positive or no association of DM with VTE risk in the general population. DM is unlikely to play a major role in VTE development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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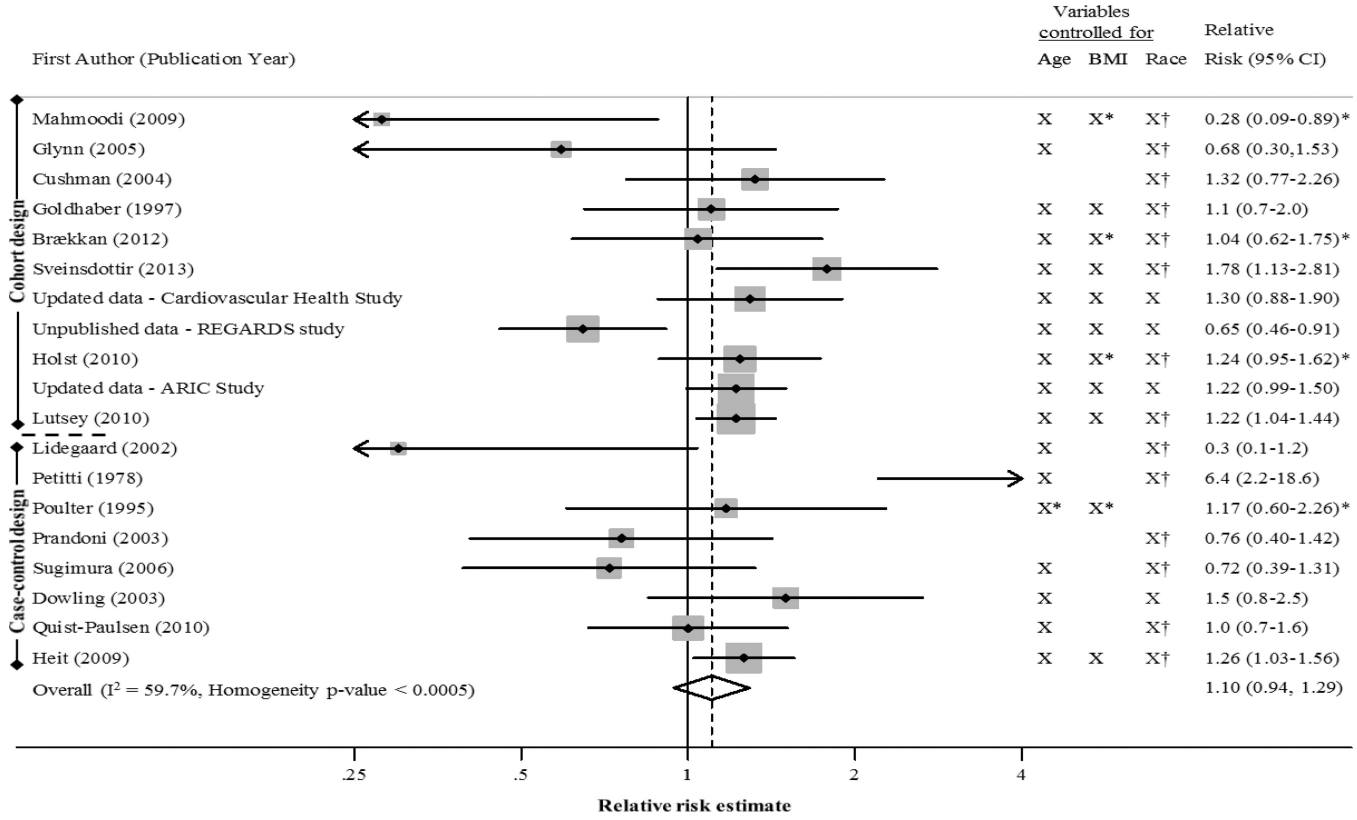

Figure 1.

Forest plot of study-specific and pooled relative risks (95% CIs) for venous thromboembolism, comparing those with DM to those without DM.

Each study is represented by a square and a horizontal line, which represents its relative risk and corresponding 95% CI, respectively. The area of the square is proportional to the weight of the study in the pooled analysis. The studies are sorted by weight in the plot and study design. The pooled random-effects estimate and its 95% CI are represented by a dashed vertical line and diamond. The vertical line at 1.0 indicates no effect of DM on venous thromboembolism risk. The table on the right side of the figure indicates whether the study-specific relative risks were controlled for potential confounding variables. *A more-fully-adjusted relative risk than originally published was obtained as a result of author query. †Study primarily involved on race-group, making statistical adjustment for race unnecessary.

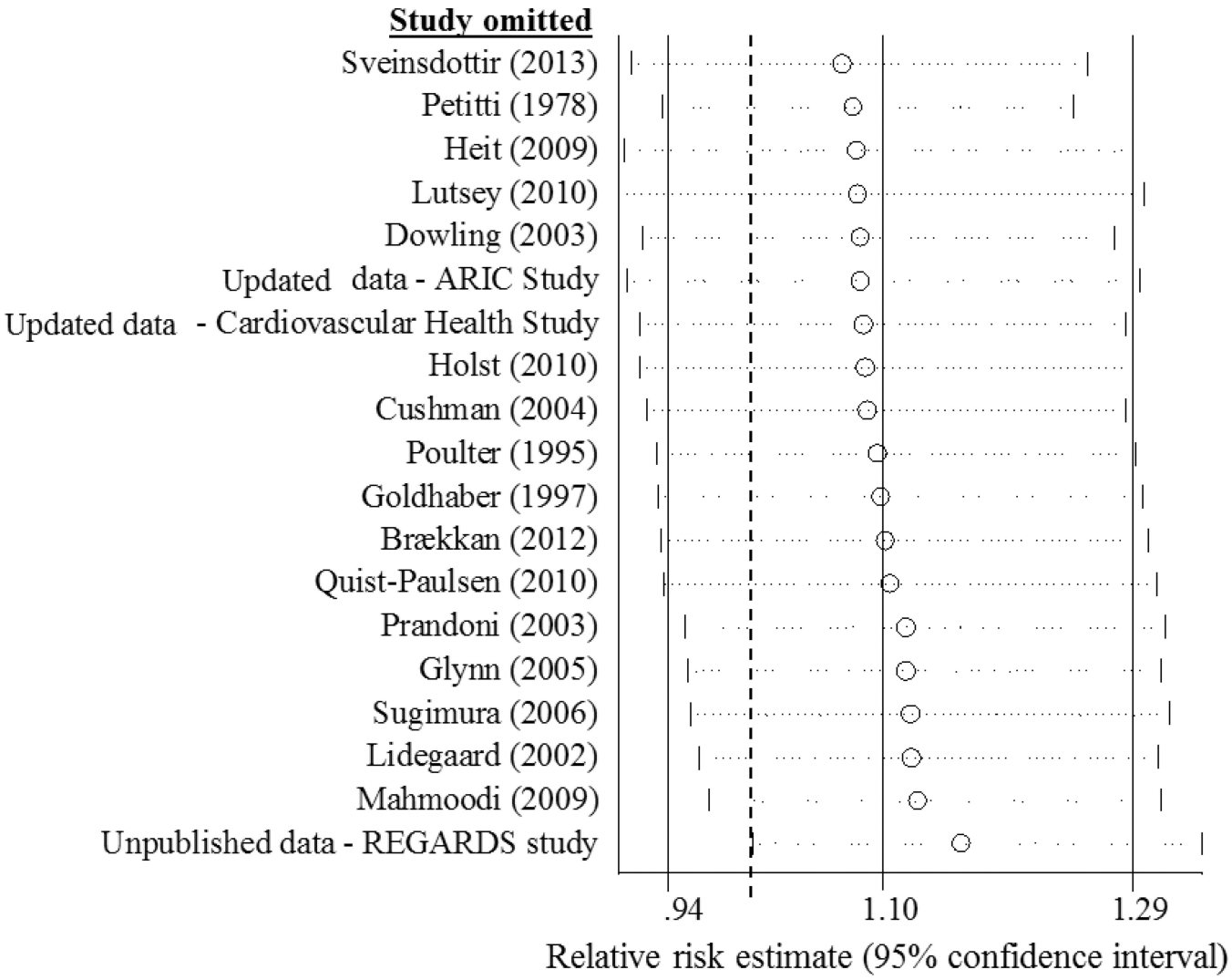

Figure 2.

Meta-analysis estimates and 95% confidence intervals, omitting one study at a time to assess the influence of any single study on the random-effects pooled estimate. The dashed vertical line at 1.0 indicates no effect of diabetes on venous thromboembolism risk.

Table 1

Characteristics of cohort studies that reported the relation between DM and VTE.

First author, publication year	Study location	Source of participants	No. of participants (cases/ cohort size)	Period of recruitment	Follow-up time, years	Age at baseline, years	BMI at baseline, kg/m^2	Distribution by race	Measurement of DM	Outcome measure
Goldhaber (1997)	United States (Nurses' Health Study)	Female registered nurses	280/112,822	1976	Max: 16	Range: 30–55	Mean: 23.8	97.6% white	Self-report	PE, based on imaging techniques (pulmonary angiogram, VQ scan) or autopsy
Cushman (2004)	United States (Women's Health Initiative)	Post-menopausal women from 40 clinical centers	243/16,608	1993–98	Mean: 5.6	Mean: 63.2, Range: 50–79	Mean: 28.4	84% white, 7% African American	Self-report	VTE, based on imaging techniques (CTPA, pulmonary angiogram, ultrasound, venogram, VQ scan) or plethysmography
Glynn (2005)	United States (Physicians' Health Study)	Male physicians	358/18,662	1982	Median: 20.1	Range: 40–84	Mean ± SD: 24.9 ± 3.0	94% white	Self-report	VTE, based on imaging techniques (pulmonary angiogram, ultrasound, venogram, VQ scan) or autopsy
Mahmoodi (2009)	Netherlands (PREVEND Study)	Inhabitants of Groningen, Netherlands	129/8,574	1997–98	Mean: 8.6	Mean ± SD: 49 ± 13	Mean ± SD: 26.1 ± 4.2	99% white	Fasting glucose level ≥7 mmol/l, nonfasting glucose level ≥11.1 mmol/l, or use of oral antidiabetic drugs. Insulin-dependent DM excluded.	VTE, based on imaging techniques (CTPA, ultrasound, VQ scan) or autopsy
Holst (2010)	Denmark (Copenhagen City Heart Study)	Inhabitants of Copenhagen, Denmark	969/18,954	1976–78, 1981–83, 1991–93, and 2002–03	Median: 19.5	Mean: 51.3	Mean: 25.0	>99% persons of Danish descent	Self-report or nonfasting glucose levels ≥11.1 mmol/l	VTE, based on national registries (ICD-8 codes 451, 451.0, 451.9, 671, 450, 673.9 for 1977–1993 and ICD-10 codes I80.1, I80.2, I80.3, O22.3, O87.1, I26.0, I26.9 since 1994)
Lutsey (2010)	Iowa (IWHS)	Iowa women from the state driver's list	2,137/40,377	1986	Max: 18	Range: 55–69	NS	99% white	Self-report	VTE, based on discharge diagnosis records (ICD codes 415.1x, 451.1x, 451.2, 451.81,

First author, publication year	Study location	Source of participants	No. of participants (cases/ cohort size)	Period of recruitment	Follow-up time, years	Age at baseline, years	BMI at baseline, kg/m^2	Distribution by race	Measurement of DM	Outcome measure
										451.9, 453.0, 453.1, 453.2, 453.3, 453.4x, 453.8, 453.9)
Brækkan (2012)	Norway (Tromsø Study)	Inhabitants of Tromsø, Norway	437/26,185	1994–95	Median: 10.8	Mean ± SD: 46 ± 5, Range: 25–97	Mean: 25.2	87.3% Norwegians, 1.6% of Sami ethnicity, 1.3% of Finnish descent, 2.2% of other ethnicities, and 7.6% without information about ethnicity	Self-report	VTE, based on imaging techniques (pulmonary angiogram, spiral CT, ultrasound, venogram, VQ scan); or autopsy
Sveinsdottir (2013)	Sweden (Malmö Preventive Study)	Male inhabitants of Malmö, Sweden	398/6,068	1974–82	Mean: 26.2	Mean: 46.8	Mean: 25.0	Almost exclusively white	Fasting glucose level ≥6.1 mmol/l or current use of any DM medication	VTE, based on Swedish hospital discharge register (ICD-8 codes 450–451, ICD-9 codes 415B or 451, and ICD-10 codes I26 and I80)
Unpublished data from ARIC	United States	Middle-aged adults from 4 communities in the United States	775/15,234	1987–89	Median: 22.5	Mean ± SD: 54.1 ± 5.8	Mean ± SD: 27.7 ± 5.3	72.9% white, 27.1% African American	Fasting glucose level ≥7 mmol/l, non-fasting glucose level ≥11.1 mmol/l, physician diagnosis of DM, or current use of any DM medication	VTE, based on imaging techniques (CTPA, pulmonary angiogram, ultrasound, venogram, VQ scan) or autopsy
Unpublished data from CHS	United States	Medicare eligibility lists from 4 communities in the United States	175/5,469	1989–90 and 1992–93	Median: 11.6	Mean ± SD: 72.8 ± 5.6	Mean ± SD: 26.6 ± 4.7	83.7% white, 16.3% African American	Fasting glucose level ≥7 mmol/l, non-fasting glucose level ≥11.1 mmol/l, physician diagnosis of DM, or current use of any DM medication	VTE, based on imaging techniques (CTPA, pulmonary angiogram, ultrasound, venogram, VQ scan), or autopsy
Unpublished data from REGARDS	United States	African Americans and whites ≥45 years of age in the contiguous United States	246/25,948	2003–2007	Mean ± SD in African Americans: 4.6 ± 1.7; Mean ± SD in whites: 4.7 ± 1.6	Mean ± SD in African Americans: 64.1 ± 9.3; Mean ± SD in whites: 65.4 ± 9.5	Mean ± SD in African Americans: 30.8 ± 6.7; Mean ± SD in whites: 28.3 ± 5.6	59.0% white, 41.0% African American	Fasting glucose level ≥7 mmol/l, non-fasting glucose level ≥11.1 mmol/l, participant report of DM, or current use of any DM medication	VTE, based on imaging techniques or autopsy

ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; CT, computed tomography; CTPA, computed tomography pulmonary angiography; ICD, International Classification of Diseases; IWHS, Iowa Women's Health Study; NS, not specified; PE, pulmonary embolism; PREVEND, Prevention of Renal and Vascular End-stage Disease; REGARDS, Reasons for Geographic and Racial Differences in Stroke; VTE, venous thromboembolism; VQ scan, ventilation-perfusion lung scan.

Table 2

Characteristics of case-control studies that reported the relation between DM and VTE.

First author, publication year	Study location	Source of cases	No. of participants (cases/ controls)	Source of controls	Period of recruitment	Response rate (cases/ controls), %	Age, years	Mean BMI ± SD in controls	Distribution by race	Measurement of DM	Outcome measure
Petitti (1978)	Walnut Creek, CA (Walnut Creek Contraceptive Drug Study)	Women who sought a general health check-up from Walnut Creek Clinic	38/8,174	Women who sought a general health check-up from Walnut Creek Clinic	1969–71	NS/NS	Range: 18–54	NS	Almost exclusively white	Self-report	Unprovoked VTE, based on discharge records and death certificates (ICD codes 450,451,453)
Poulter (1995)	21 centers across Africa, Asia, Europe, and Latin America (WHO CCS Study)	Women admitted to participating hospitals	1,143/2,998	Women admitted to participating hospitals	1989–1993	>97/>98	Range: 20–44	23.8 ± NS	Race distribution not reported, but distribution by geographic area was: 36% European, 13% African, 8% Asian, 43% Latin American	Self-report	Unprovoked VTE, based on imaging techniques (pulmonary angiography, radioisotope studies, ultrasound, venogram, V/Q scan), signs/symptoms in the absence of other likely cause, or autopsy
Dowling (2003)	Atlanta, GA (GATE Study)	Patients admitted to 2 university-owned hospitals	370/250	Patients from a university-affiliated primary care clinic	1997–2001	57/49	Control mean: 49.5	26.1 ± NS	Controls: 36% African American, 64% white	Self-report	VTE, based imaging techniques (angiogram, CT, CTPA, MRI, ultrasound, venogram, VQ scan)
Lidegaard (2002)	Denmark	Women admitted to Danish hospitals	987/4,054	Women in Denmark's population registry	1994–98	87.2/89.7	Range: 15–44	22.2 ± NS	94% of women in Denmark are of Danish descent	Self-report	VTE, based on discharge diagnosis, with confirmation from the department that was responsible for diagnosis

First author, publication year	Study location	Source of cases	No. of participants (cases/ controls)	Source of controls	Period of recruitment	Response rate (cases/ controls), %	Age, years	Mean BMI ± SD in controls	Distribution by race	Measurement of DM	Outcome measure
Prandoni (2003)	Padua, Italy	Outpatients admitted to University of Padua Medical School's institution	299/150	Outpatients admitted to University of Padua Medical School's institution	1996–2001	99/NS	Control mean ± SD: 65.4 ± 15.7	Obesity - number (%): 16 (10.7%)	90.7% Italian	Fasting glucose level ≥7 mmol/l on at least 2 occasions, ≥11.1 mmol/l after an oral glucose tolerance test, or current use of any DM medication	Proximal DVT, based on imaging techniques (ultrasound)
Sugimura (2006)	Japan	Patients admitted to university clinics and to hospitals with more than 100 beds	204/204	Patients admitted to university clinics and to hospitals with more than 100 beds	2004	NS/NS	Control mean ± SD: 64.3 ± 15.2	22.8 ± 3.8	98.5% Japanese	NS	PE, based on imaging techniques (CTPA, MRI, pulmonary angiography, VQ scan) or autopsy
Heit (2009)	Olmsted County, Minnesota (Rochester Epidemiology Project)	Olmsted County residents	1,922/2,115	Olmsted County residents	1976–2000	NS/NS	Control mean ± SD: 64.6 ± 19.2	26.3 ± 5.3	96% white	Physician diagnosis in medical record	VTE, based on imaging techniques (CTPA, CT venogram, MRI, pulmonary angiography, ultrasound, venogram, VQ scan) plethysmography, autopsy, or pathology examination of removed thrombus
Quist-Paulsen (2010)	Nord-Trøndelag County, Norway (HUNT 2 Study)	HUNT 2 cohort	515/1,476	HUNT 2 cohort	1995–2001	NS/NS	Control mean ± SD: 66.3 ± 14.6	27.0 ± 4.2	>97% white	Self-report	VTE, based on imaging techniques (CTPA, CT scan, ultrasound, venogram, VQ scan) or autopsy

CT, computed tomography; DVT, deep vein thrombosis; GATE, Genetic Attributes and Thrombosis Epidemiology; NS, not specified; MRI, magnetic resonance imaging; PE, pulmonary embolism; VTE, venous thromboembolism; WHO CCS, World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.